REMARKS

This invention is drawn to a method for isolating an intact clone of a target nucleic acid fragment having a known characteristic, from a group of fragments. The steps of the invention comprise preparing an initial library of clones from a number of fragments, subjecting the library to a plurality of restrictions, screening the group of monodigested libraries for the known characteristics, subjecting the initial library to a number of the plurality of restriction enzymes, and isolating an intact clone.

Claims of this case are subject to restriction requirement. Specifically, Claims 21 and 22 have been deemed drawn to a non-elected invention. Accordingly, Claims 21 and 22 have been canceled.

Applicant notes with appreciation the withdrawal of the objections to Claims 1 and 19 over various informalities as well as other withdrawn rejections.

Claim 11 remains objected to under 37 C.F.R. § 1.75(c). Claim 11 has now been canceled. Accordingly, this rejection has been obviated.

Claims 1-19 have been rejected "under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

It appears that this rejection stems from the amendment to Claims 1 and 16 to recite that the claimed process is "useful to isolate an intact nucleic acid fragment and diagnose genetic disease." The objectionable language has been removed, and Applicant believes that this rejection has thereby been obviated.

However, Applicant expects that this will give rise to a reinstatement of the rejection under 35 U.S.C. § 101 which was set forth in the Office Action dated April 23, 2001. There, Claims 1-19 were rejected "under 35 U.S.C. § 101 because the claimed processes (methods) are not supported by either a specific and/or substantial asserted utility or a well established utility." Applicant respectfully disagrees with such an assessment. The rejection later states, "the instant specification discloses that the claimed methods are useful for screening for finding sequences with enzymatic activity or homology to other sequences which can then be isolated, sequenced, transfected etc.; e.g. see page 1 and abstract." This is correct. As pointed out by the Examiner, the present application discloses a claimed method useful for screening to find sequences with enzymatic activity or homology to other sequences which can then be isolated, sequenced, or transfected. Thus the present invention pertains to a process or method for screening, not to a particular nucleotide fragment or process for finding a particular nucleotide fragment, the usefulness of which might be considered dubious.

The Office Action cites *Brenner v. Manson* 383 U.S. 519, 148 USPQ 689 (1966) for the proposition that merely disclosing the ability to make (or isolate) a compound or compounds is in itself insufficient utility to satisfy either 35 U.S.C. § 101 or 112. This case is clearly distinguishable from *Brenner v. Manson.* In that case, the process pertained to a method of making a steroid whose use was unknown. Thus the underlying compound had no usefulness and therefore the method of making the compound had no real usefulness either. In the present case, the application pertains to a method for isolating nucleotide fragments. While it is true that the method of the present invention

can be used to isolate fragments with no known utility, it can also be used to isolate fragments with known utility. As such, contrary to the case in *Brenner*, the method of the present invention has utility in isolating DNA fragments with known utility. Accordingly the present invention has utility as well. That specific utility is to isolate a target nucleic acid sequence from a mixture of DNA fragments of similar size.

In the present case, the screening method is useful in that it can be used in conjunction with other method steps to evaluate materials other than the screening method itself. It can for instance be used to screen for a fragment containing a known gene, such as a gene causing a genetic disease. Such diseases include cystic fibrosis or phenylketonuria.

As a specific example, in the case of phenylketonuria or some other gene linked enzymatic deficiency, it would be useful to identify the gene which codes for phenylalanine hydroxylase in a healthy individual so that the defective gene can be isolated and characterized. Accordingly, the initial library of clones would be screened for phenylalanine hydroxylase activity to insure the presence of a full gene coding for the enzyme. The library would then be subjected to up to 70 or more restriction enzymes, individually, in parallel, resulting in 70 separate, monodigested libraries. The resulting group of monodigested libraries would then be similarly screened for phenylalanine hydroxylase production and activity. Of those, on average 50 libraries would show activity. This corresponds to approximately 50 restriction enzymes which did not cleave the active gene.

The initial library is then subjected to those approximately 50 restriction enzymes which did not cleave the active portion of the DNA molecule (that is the restriction enzymes to which the target fragment is insensitive). This would produce a multidigested library having an intact clone of the target nucleic acid fragment. That fragment can then be isolated and thus a DNA fragment including a coding region for phenylalanine hydroxylase would be isolated. Having the coding region for this enzyme would in itself be useful, but it could further be used to identify individuals having a defective region and therefore subject to developing phenylketonuria. Thus the process of the present invention is useful for isolating intact clones having a known characteristic.

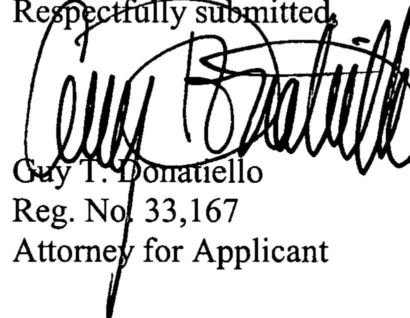
The specification in the present case does not limit the DNA fragments with which the present invention can be used. This should come as no surprise since the present invention can be used with nearly any DNA fragment having a characteristic which can be screened.

The Action states, "one using the invention must determine the characteristic to be screened for, the method(s) of screening, select the source(s) of target nucleic acid fragments..." Applicant respectfully submits that the Action mischaracterizes the invention. One using the invention is not required to determine the characteristic to be screened for. Rather the invention is useful to someone skilled in the art who desires to screen for a particular characteristic. This is akin to saying that to use a car one must determine a place to which one wishes to be transported. This is incorrect. Rather, one wishing to travel uses a car for transportation. One who has no wish to travel has no need for a car, just as one skilled in the art having no characteristic to screen for would have no

use for the present invention. That in no way negates the usefulness of the present invention. It is useful to those skilled in the art who desire to screen a DNA library for a particular characteristic; it is useful.

Accordingly, Applicant believes that the utility of the present invention has been demonstrated and respectfully requests that this rejection be withdrawn and this case be allowed to issue.

Respectfully submitted,



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In the Claims (Clean copy as amended)

1. (Twice amended) A process for isolating an intact clone of one target nucleic acid fragment having a known characteristic, from a number of fragments, said process comprising:

a) preparing an initial library of clones from said number of fragments using a vector containing no more than a pre-determined number of known restriction sites;

b) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of monodigested libraries;

c) screening said group of monodigested libraries for said known characteristic to detect the presence of intact target fragments, to thereby determine those restriction enzymes to which said target fragment is insensitive;

d) subjecting said initial library to substantially all of said plurality of restriction enzymes to which said target fragment is insensitive, to produce a multidigested library having an intact clone of the target nucleic acid fragment; and

e) isolating an intact clone from the multidigested library.

2. (Previously amended) The process of Claim 1 wherein said plurality of restriction enzymes comprises at least 10 restriction enzymes.

3. (Previously amended) The process of Claim 1 wherein said plurality of restriction enzymes comprises at least 50 restriction enzymes.

4. (Previously amended) The process of Claim 1 wherein said plurality of restriction enzymes comprises at least 70 restriction enzymes.

5. (Previously amended) The process of Claim 1 wherein said pre-determined number of known restriction sites is four.

6. (Previously amended) The process of Claim 1 wherein said pre-determined number of known restriction sites is three.

7. (Previously amended) The process of Claim 6 wherein at least one of said three sites is different from, and flanked by, said two remaining sites.

8. (As filed) The process of claim 1 wherein said restriction enzymes have cleavage sites from 5 to 6 nucleotides in length.

9. (Previously amended) The process of Claim 1 including the further step of transforming and replicating said intact clone of the target nucleic acid fragment.

10. (Previously amended) The process of Claim 9 including the further step of isolating said intact clone.

11. (canceled).

12. (Previously amended) The process of Claim 1 comprising, after step b), the further step of transfecting said monodigested libraries in cellular hosts.

13. (Previously amended) The process of Claim 1 comprising the further step of verifying the presence of said target fragment in said initial library by transfecting in a cellular host and screening said transfected host for the presence of said target fragment.

14. (Previously amended) The process of Claim 1 comprising the further step of verifying the presence of said target fragment in said multi-digested library by

transforming said library and screening said transformed library for the presence of said target fragment.

15. (Previously amended) The process of Claim 1 wherein said number of fragments contains up to 10^8 fragments, each from about 0.1kb to 5kb in size.

16. (Twice amended) A process for isolating an intact clone of one target nucleic acid fragment having a known characteristic, from a group of fragments, said process comprising:

a) preparing an initial library of clones from said number of fragments using a vector containing no more than a pre-determined number of known restriction sites;

b) verifying the presence of said target fragment in said initial library by transfecting in a cellular host and screening said transfected host for the presence of said target fragment;

c) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of monodigested libraries;

d) independently transfecting said monodigested libraries;

e) screening said group of monodigested libraries for said known characteristic to detect the presence of intact target fragments, to thereby determine those restriction enzymes to which said target fragment is insensitive;

f) subjecting said initial library to substantially all of said plurality of restriction enzymes to which said target fragment is insensitive, to produce a multidigested library having an intact clone of the target nucleic acid fragment; and

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g) transforming said multidigested library.

17. (Previously amended) The process of Claim 16 wherein said restriction enzymes have cleavage sites from 5 nucleotides in length.

18. (As filed) A process for isolating an intact clone of one target nucleic acid fragment having a known characteristic, from a group of fragments, said method comprising:

a) preparing an initial library of clones from said group of fragments using a vector containing no more than a predetermined number of known restriction sites;

b) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of mono-digested libraries;

c) transforming said monodigested libraries into bacteria;

d) culturing said bacteria to produce digested libraries substantially free of cleaved products, cleaving each digested library to produce digestion products, depositing said products in an agarose gel well, migrating said products, transferring said products onto a membrane, hybridizing said transferred products with a probe, to thereby determine those restriction enzymes to which said target fragment is insensitive; and

d) subjecting said initial library to substantially all of said plurality of restriction enzymes to which said target fragment is insensitive, to produce a multi-digested library having an intact clone of the target nucleic acid fragment.

19. (Previously amended) A method for producing a series of monodigested libraries from a group of fragments, said method comprising:

a) preparing and initial library of clones from said group of fragments using a vector containing no more than a pre-determined number of known restriction sites; and

b) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of monodigested libraries.

20. (As filed) The group of monodigested libraries produced by the process in claim 19.

21. (canceled)

22. (canceled)